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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,048	03/28/2007	Karl-Hermann Schlingensiepen	4052.003	4668

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,048	SCHLINGENSIEPEN ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/18/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-45* is/are pending in the application.

4a) Of the above claim(s) *34-38 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-33 and 39-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence Validation Report*.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 3/18/2010 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/18/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

With entry of the amendment filed on 3/18/2010, claims 23-45 are pending in the application.

Claims 34-38 and 45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/24/2008.

Claims 23-33 and 39-44 are examined herein.

Elections/Restrictions

The previous Action acknowledged Applicant's election without traverse of "melanoma" as the type of cancer. See Applicant's reply filed 7/13/2009. An earlier Action had also acknowledged Applicant's election without traverse of Group I, claim(s) 23-34 and 38-45, drawn to a method for treating cancer, comprising administering at least one oligonucleotide, and to an antisense oligonucleotide and pharmaceutical composition thereof. Also acknowledged was Applicant's further election without traverse of "carcinoma," and with traverse of "TGF-beta 2" and "SEQ ID NO:30."

Specification/Sequence Compliance

The amendment to the specification filed 5/18/2010, adding SEQ ID No. identifiers, is noted and has been entered into the application. However, the disclosure remains objected to because the new or substitute sequence listing filed 5/18/2010 is defective for the reasons given on the attached Sequence Validation Report. Accordingly, the application continues to fail to comply with the requirements of 37 CFR 1.821 through 1.825. Correction is required.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Claim Objections

Applicant is advised that should claim 39 be found allowable, claim 42 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-33 and 39-44 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of copending U.S. Patent 7,667,027 in view of:

1. Reintgen (U.S. Patent 6,153,388);
2. Mintz (U.S. Patent 5,550,316);
3. Paradise et al. (U.S. Patent 4,999,339);
4. Swift (U.S. Patent 5,843,974);
5. Aylward (U.S. Patent 6,787,161);
6. Brandt et al. (U.S. Patent 5,610,280); and
7. McCracken (U.S. Patent 5,369,527).

Although the conflicting claims are not identical, they are not patentably distinct.

MPEP 804 states those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in *Vogel* recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is

not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

U.S. Patent 7,667,027 claims an antisense oligonucleotide having the sequence of SEQ ID NO:83. The claims do not define or disclose the nucleotide sequence or utility of the oligonucleotide. Accordingly, one of skill would necessarily need to refer to the relevant portions of the specification to understand how to make and use the claimed invention, SEQ ID NO:83, in the manner intended by the inventor and in the manner required by 35 USC 101 and 112, first paragraph.

One would therefore refer to the sequence listing to determine that SEQ ID NO:83 has the sequence 5'-ctggcttttgggtt-3'. One would further refer to any and all sections of the specification describing SEQ ID NO:83 or the oligonucleotides of the invention to determine the how to use, including the best mode for using SEQ ID NO:83. One would find from page 1, first paragraph, and page 4, first full paragraph, that the oligonucleotides disclosed by the application, including SEQ ID NO:83, hybridize with the gene enconding TGF-β. One would further understand from page 11 bridging to page 12 that the antisense oligonucleotides disclosed and claimed therein can be used for the treatment of "skin carcinogenesis."

As evidenced by at least references 1-7, above, at the time of invention, melanoma was a recognized form of skin cancer. It would therefore have been prima facie obvious to one of skill in the art at the time of invention to use SEQ ID NO:83 to treat any skin carcinogenesis, including melanoma, a recognized form of skin cancer.

For example, Reintgen taught that "Malignant melanoma is a form of skin cancer that can develop from melanocytes..." (col. 1, lines 13 and 14). Reintgen further stated that

"Histopathologists usually examine and determine the extent of melanomas *of the skin* by measuring the thickness of the tumor and the level of penetration into *the skin*..." (col. 1, lines 57-59, emphasis added).

McCracken taught that "indications of skin cancer, specifically melanoma, can be detected visually..." (col. 1, lines 14 and 15).

Mintz taught that "Primary malignant melanoma of the skin is the leading cause of death from any skin disease..." (col. 1, lines 21-22). Mintz further taught that "Melanoma has been estimated to account for 1 percent of all skin cancers..." (col. 1, lines 25-27).

Paradise et al. taught that "Seventy-five percent of skin cancer deaths in the United States are due to malignant melanoma..." (col. 1, lines 14-16).

Swift taugh that "Melanoma is a malignant tumor of melanocytes largely located in the skin." (col. 1, lines 5-8). It is also said "The greatest danger with melanoma is metastases..." (col. 1, line 15).

Aylward taught that "There is a strong association between exposure of the skin to the ultraviolet light component of sunlight and the development of *skin cancers*, such as malignant melanoma and non-melanoma *skin cancers*..." (col. 1, lines 23-27; emphasis added).

Brandt et al. taught that "Melanoma, a tumour of the skin, is an extremely aggressive tumour. Especially metastasing melanoma can scarcely any longer be successfully treated by conventional methods. Therefore, there is a great need to find new therapeutics which can be used for the treatment of melanomas." (Col. 1, lines 9-14).

Accordingly, with regard to Applicant's remarks filed 3/18/2010, the prior art is replete with references to melanoma as a form of skin cancer, and as a cancer of the skin, and as a

cancer in the skin. In view of the disclosed utility for SEQ ID NO:83 as an oligonucleotide for the treatment of skin carcinogenesis, one of skill would reasonably have concluded that the oligonucleotide could be used to treat a skin carcinogenesis such as any of those known in the art. An would have used SEQ ID NO:83 consistent with manner of making and using the oligo disclosed in the specification of 11/647586.

Additionally, one of skill would instantly have recognized that SEQ ID NO:36 of the instant application, recited in claims 26, 27, 33, and 41, is identical to SEQ ID NO:83. See alignment below. One would therefore have considered the instantly claimed method of using SEQ ID NO:36 to be obvious in view of the utility of SEQ ID NO:83 claimed in U.S. Patent 7,667,027.

Noting Applicant's remarks filed 3/18/2010, the fact that one of skill would not have known or expected that SEQ ID NO:83 or any other oligo disclosed by U.S. Patent 7,667,027 would inhibit metastases, or that one of skill would not consider using SEQ ID NO:83 to inhibit metasases is irrelevant, since one of skill would have considered using SEQ ID NO:83 to treat a skin carcinogenesis, including any of those known in the art, including melanoma and non-melanoma skin cancers (i.e., carcinogenesis) in the manner taught by U.S. Patent 7,667,027. In practicing this use, one of skill would necessarily obtain all biological effects inherent to the compound (the oligonucleotide comprising SEQ ID NO:83), regardless of whether one of skill had recognized the inherent effects or not (MPEP 2112). A compound and its properties are inseparable (MPEP 2112.01). As evidenced by at least instant claim 27, SEQ ID NO:36, and therefore, SEQ ID NO:83 does, in fact, inhibit metastases in a subject. Therefore the effect is inherent. One of skill would have had reason to use SEQ ID NO;83 to treat any melanoma or

non-melanoma skin carcinogenesis because U.S. Patent 7,667,027 teaches the treatment of skin carcinogenesis is one utility for the claimed sequence comprising SEQ ID NO:83 and because one of skill would instantly have recognized that skin cancers include melanoma and non-melanoma cancers. Even if the melanoma treated has not yet metastasized at the time of treatment, the method now claimed is still rendered obvious by U.S. Patent 7,667,027 because the inhibitory effect is, nevertheless, present and intrinsically associated with the oligonucleotide.

Alignment of SEQ ID NO:83 with instant SEQ ID NO:36:

```
                                     RESULT 4
US-10-591-048-36
; Sequence 36, Application US/10591048
; Publication No. US20070155685A1
; GENERAL INFORMATION:
;  APPLICANT: Antisense Pharma GmbH
;  TITLE OF INVENTION: Pharmaceutical composition
;  FILE REFERENCE: A30002
;  CURRENT APPLICATION NUMBER: US/10/591,048
;  CURRENT FILING DATE:  2006-08-28
;  PRIOR APPLICATION NUMBER: EP 04 004 478.6
;  PRIOR FILING DATE: 2004-02-27
;  PRIOR APPLICATION NUMBER: US 60/558,135
;  PRIOR FILING DATE: 2004-04-01
;  NUMBER OF SEQ ID NOS: 107
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 36
;  LENGTH: 14
;  TYPE: DNA
;  ORGANISM: Artificial Sequence
;  FEATURE:
;  OTHER INFORMATION: Antisense to TGF-beta 2
US-10-591-048-36

  Query Match             100.0%;  Score 14;  DB 19;  Length 14;
  Best Local Similarity   100.0%;  Pred. No. 4.8e+03;
  Matches   14;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CTGGCTTTTGGGTT 14
              ||||||||||||||
Db          1 CTGGCTTTTGGGTT 14
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Accordingly, it would have been immediately obvious to administer the antisense defined by claims 1 and 2 of U.S. Patent 7,667,027 to a subject in the manner claimed, including such subjects having skin cancer such as melanoma, to treat melanoma. All effects inherent to the administration of the oligonucleotide would be obtained thereby, including those recited in the instant claims (MPEP 2112).

***

The provisional rejection of Claims 23-33 and 39-44 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-26 of copending Application No. 10/146058 is withdrawn in view of the abandonment of 10/146058.

***

The provisional rejection of Claims 23-33 and 39-44 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-7, 18, 20-24 of copending Application No. 10/581547 is withdrawn in view of the abandonment of 10/581547.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of the recitation "and active derivatives thereof." One of skill in the art would not know the metes and bounds of the term because the specification has not clearly defined how and to what degree a compound can differ from the claimed compounds and still be considered an active derivative within the scope of the claims. The term reasonably embraces a multitude of structurally distinct nucleic acid-based compounds, including compounds comprising any type of non-nucleic acid element, group, or moiety, and the specification does not reasonably enable one of skill to envision the group of compounds specifically included or excluded by this limitation.

Correction is required.

Claim 41 is rejected as indefinite because the limitation "said oligonucleotide" in line 1 lacks sufficient antecedent basis in the claim.

Claim Rejections - 35 USC § 112, first paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 24, 28-31, 39, 40, and 42-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn to a method for treating cancer, comprising administering at least one oligonucleotide to a subject, wherein the oligonucleotide "inhibits formation of metastases in

said subject," "inhibits the synthesis of proteins involved in the formation of metastases," or, in a slightly more specific embodiment, "inhibits the production of a transforming growth factor." In certain embodiments, the cancer and thereby the particular subject in which the formation of metastases is inhibited may be any the many different cancers recited in claims 28-30, 39, 42, and 44, including melanoma. In certain embodiments, the claims embrace and require the administration of any "TGF-beta 2 antagonist" to treat cancer.

Thus, the claims are extremely broad, encompassing the use of any oligonucleotide of essentially any length and any nucleotide sequence and/or chemical composition that fulfills the function required by the claim: inhibition of the metastasis formation, inhibition of the synthesis of proteins involved in metastasis, and inhibition of "a" transforming growth factor. To be sure, claim 23, 28-30, 43, and 44 are not even limited to antisense oligonucleotides, but include any type of oligonucleotide, including any triple helix forming oligo, any aptamer, ribozyme, or, for example, decoy oligonucleotide and virtually any other conceivable oligonucleotide known or yet to be discovered that has the function recited by the claim. Additionally, certain claims embrace and seek exclusive rights to the use of any "TGF-beta 2 antagonist" for treatment of any of the cancers listed. The limitation TGF-beta 2 antagonist embraces any organic or inorganic compound, large or small molecule, protein, peptide, antibody, nucleic acid, lipid, or carbohydrate, and any active derivative thereof, and clearly any conceivable known or yet-to-be-discovered substance that antagonizes/inhibits TGF-beta 2, including any TGF-β2 binding protein, receptor related inhibitors, binding peptides, TGF-β antibodies, regulators of TGF-beta2 expression, Smad inhibitiors, and any active derivatives thereof (claim 40).

Adequate written description does not exist in the instant application for all these substances. Therefore adequate written description does not and cannot exist for all the methods of using these substances. The substances required for the methods are recited in terms of their function only, there is no art-recognized correlation between the structure and function, and the specification does not provide the support needed to enable one skilled in the art to predict with a reasonable degree of confidence the structure of the claimed inventions from a recitation of function.

Rather, the specification as filed is much more narrowly drawn to the use of a specific set of antisense oligonucleotides (SEQ ID NO: 1-68) that specifically inhibit the expression of TGF-beta 1, 2, and/or 3 and thereby the formation of metasases (page 3, page 10 bridging to 11; and see Example 5 and following examples regarding Scratch Assay). While the specification may hypothesize that any agent, including any TGF-β2 antagonist, may be used to produce the same effect, the specification does not describe any other such agents, as by providing the full or partial structures of sufficient species representative of the genus or by describing some structure common to the genus of proteins, nucleic acids, or small molecules that will have the function required by the claims. In the absence of sufficient identifying features of the substances/antagonists required by the claims, the specification and claims represent nothing more than an invitation to carry out the research necessary to identify the agents, oligonucleotides, and antagonists that have the function required by the claims. On the basis of the current disclosure, apart from those antisense oligonucleotides specifically identified by the specification, one of skill could not reasonably envision, without resoreting to trial and error, *de novo* experimentation and screening, the substances, oligonucleotides, and antagonists required

by the claims. The specification and claims represent nothing more than a wish to know the substances without providing the distinguishing characteristics of the substances. This does not satisfy the written description requirement for the claimed genus of methods. "…[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion (Brenner, Comr. Pats. v. Manson, 148 USPQ 689 (U.S. 1966)).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

A disclosure in a parent application that merely renders the later- claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations. *See Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

In the instant case, the specification does not clearly allow persons of ordinary skill in the art to recognize that Applicants invented what is now claimed. Apart from the antisense oligonucleotides specifically identified by SEQ ID NO, as in claims 26 and 27, or by specific gene target, as in claim 25, the application does not enable the skilled artisan to clearly envision the detailed chemical structure of the encompassed genus of substances that inhibit the formation of metastases except by resorting to empirical testing.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures,

diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

MPEP 2163 states in part that "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

In the instant case, applicants have not satisfied either of these criteria. That is, apart from claims 25-27, the instant application discloses no correlation between the structure of an oligonucleotide and its ability to inhibit the formation of metastases, or between the structure of any substance and its ability to antagonize TGF-β2. And one could not reasonably predict the structure of any other oligonucleotide or substance from the sequences of SEQ ID NO:1-68.

Indeed, in traversing the 35 USC 103 rejection in view of Reed et al., Applicant states in the remarks filed 3/18/2010 that Reed discloses that the use of a TGF-β antisense nucleotide is not reliable for inhibiting the formation of metastases in vivo, implying there is some level of unpredictability in the genus required by the methods. Applicant however presents no evidence other than the statement Reed does not test in vivo that the oligos will not produce the same result in vivo.

While the specification adequately describes those oligonucleotides that inhibit TGF-β1, 2, or 3 for inhibiting metastasis by fully setting forth their structures and functions, and by describing the materials and methods needed to make and use such agents, adequate written description does not exist for the virtually unlimited number of other inhibitors and antagonists in the claimed genus. Thus, applicants have not shown possession of the claimed methods using all such agents, as now generically proposed by the claims.

Accordingly, only methods comprising the use of antisense oligonucleotides that inhibit the expression of TGF-β2, such as any of those defined by claims 26 and 27, meet the written description requirement.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (c) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23-29 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Schlingensiepen et al. (US Patent 6,455,689) "Antisense-oligonucleotides for transforming growth factor-β (TGF-β)".

Schlingensiepen et al. disclosed methods for making and using antisense oligonucleotides for inhibiting the expression of TGF-β2 and treating neurofibroma, malignant glioma, skin carcinogenesis, and esophogeal and gastric carcinomas (see entire disclosure, including col. 6, lines 8-30). Instant claim 28 expressly embraces treatment of esophageal, neurofibroma(s), and skin cancer. Claim 29 includes esophageal cancer. Exemplary antisense oligonucleotides expressly recommended by Schlingensiepen et al. for the treatment of these cancers include those comprising SEQ ID Nos. 1-137, each of which is said to hybridize with the gene encoding TGF-β1, 2, and/or 3 (col. 2, lines 31-56). As shown by the alignment below, the antisense oligonucleotide of SEQ ID NO:72 is identical to instantly recited SEQ ID NO:30 (col. 2).

As evidenced claims 26, 27, 33, and 41 of the instant application, the antisense oligonucleotide of SEQ ID NO:30, and therefore of SEQ ID NO:72, is an oligonucleotide that inhibits the formation of metastases and production of TGF-beta2. As evidenced by claims 28 and 29, which recite the method of claim 23 for treating esophogeal and neurofibroma cancer, the administration of an oligonucleotide within the scope of claim 23, such as that comprising SEQ ID NO:72 (SEQ ID NO:30), will treat esophageal and neurofibroma cancers and inhibit the formation of metastases in such cancers. As evidenced by page 1, line 13, of the specification, TGF-β is in fact a protein whose synthesis is involved in metastasis.

Therefore, in using any of the antisense oligonucleotide compounds of SEQ ID NO:1-137 in Schlingensiepen et al. to treat neurofibroma, malignant glioma, skin carcinogenesis, esophogeal or gastric carcinoma, in the manner taught by Schlingensiepen et al., the practitioner will necessarily and always obtain all biological effects inherent to the antisense oligonucleotide compound, including those recited by the instant claims. A compound and its properties are inseparable (MPEP 2112). The compound and all properties intrinsically associated with the compound and its disclosed method of use are disclosed even if the prior art did not expressly recognize each and every property.

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). "[T]he PTO can require an

applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on 'inherency' under 35 U.S.C. 102, on '*prima facie* obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Accordingly, Schlingensiepen et al. disclosed a method within the scope of what is now claimed.

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RESULT 1
US-08-535-249-72
; Sequence 72, Application US/08535249
; Patent No. 6455689
;  GENERAL INFORMATION:
;    APPLICANT:  Schlingensiepen, Georg-Ferdinand
;    APPLICANT:  Brysch, Wolfgang
;    APPLICANT:  Schlingensiepen, Karl-Hermann
;    APPLICANT:  Schlingensiepen, Reimar
;    APPLICANT:  Bogdahn, Ulrich
;    TITLE OF INVENTION:  Antisense-oligonucleotides for the treatment of
;    TITLE OF INVENTION:  immuno-suppressive effect of transforming-growth-factor beta (TG
;    NUMBER OF SEQUENCES:  137
;  INFORMATION FOR SEQ ID NO:  72:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  18 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  unknown
;      TOPOLOGY:  unknown
;    MOLECULE TYPE:  DNA (genomic)
;    ANTI-SENSE:  YES
US-08-535-249-72

  Query Match             100.0%;  Score 18;  DB 3;  Length 18;
  Best Local Similarity   100.0%;  Pred. No. 28;
  Matches   18;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CGGCATGTCTATTTTGTA 18
              ||||||||||||||||||
Db          1 CGGCATGTCTATTTTGTA 18
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Claims 23-25 and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Monia et al. (US 2004/0006030) "Antisense modulation of TGF-β2 expression."

Monia et al. disclosed methods and materials for making and using nuclease resistant antisense oligonucleotides to inhibit the expression of TGF-β2 in a cell in vivo to treat hyperproliferative diseases such as cancer in a subject (claim 17, and supporting disclosure). Monia et al. taught the association between TGF-β2 expression and various forms of cancer (paragraph 12), including melanoma, stating the prior art had disclosed that TGF-beta 2 was found to be expressed in all uveal melanomas tested and found to correlate with colon cancer progression (par. 12). It is taught the antisense oligonucleotides disclosed therein may be used in diagnostics, therapeutics, and prophylaxis, and that antisense oligonucleotides in general have been employed as therapeutic moieties in the treatment of disease states in animals and man. Pharmceutical formulation and methods of administering oligonucleotide pharmaceutical formulations are disclosed in detail (pp. 10-20). Antisense oligonucleotide drugs, including ribozymes, have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established that oligonucleotides can be useful therapeutic modalities that can be configured to be useful in treatment regimes for treatment of cells, tissues and animals, especially humans (par. 50).

All effects inherent to the use of antisense oligonucleotides that inhibit TGF-β2, including those recited in the instant claims, such as inhibition of metastasis formation, would necessarily be obtained by the administration of such oligonucleotides, since a compound and its properties are inseparable, and since, as evidenced by instant claim 25, the inhibition of TGF-β2 inhibits formation of metastases (MPEP 2112).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28-33, 39-42, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlingensiepen et al. (US Patent 6,455,689) "Antisense-oligonucleotides for transforming growth factor-β (TGF-β)", as applied to claims 23-29 and 43 above, and further in view of:

1. Reintgen (U.S. Patent 6,153,388);
2. Mintz (U.S. Patent 5,550,316);
3. Paradise et al. (U.S. Patent 4,999,339);

4. Swift (U.S. Patent 5,843,974);
5. Aylward (U.S. Patent 6,787,161);
6. Brandt et al. (U.S. Patent 5,610,280);
7. McCracken (U.S. Patent 5,369,527);
8. Fakhrai et al. (US Patent 6,120,763)"Compositions and methods for enhanced tumor cell immunity in vivo";
9. Monia et al. (US 2004/0006030) "Antisense modulation of TGF-β2 expression";
10. Reed et al. (1994) "Expression of transforming growth factor-beta 2 in malignant melanoma correlates with the depth of tumor invasion. Implications for tumor progression" *Am J Pathol.* Jul;145(1):97-104;

Schlingensiepen et al. is relied on for the reasons given above in the rejection of claims 23-29 and 43 under 35 USC 102(b).

Schlingensiepen et al. does not teach administering TGF-β1, 2, and/or 3-specific antisense oligonucleotides to subjects having melanoma.

However, it would have been *prima facie* obvious to use any of the anti-TGF-β oligonucleotides disclosed by Schlingensiepen et al. to treat a melanoma in a subject in view of the fact that Schlingensiepen et al. specifically teaches the antisense are useful for treatment of skin carcinogenesis and in view of the fact that melanoma was a well recognized form of skin cancer at the time of invention, as evidenced by references 1-7, above, each of which is relied on for the reasons given above in the rejection of the claims on the grounds of double patenting.

Furthermore, as shown by Monia et al., Fakhrai et al., and Reed et al. the prior art had taught a strong correlation between TGF-β2 expression/production and malignant melanoma and specifically recommended using antisense oligonucleotides to inhibit the expression of TGF-β and treat cancer.

For example, Fakhrai et al. disclose and claim a method for prolonging survival of a subject having melanoma, comprising administering to said subject a therapeutically effective amount of genetically modified cells containing a genetic construct expressing an antisense oligonucleotide that inhibits the expression of TGF-β, including TGF-β2 (see disclosure and claims).

Monia et al. disclosed methods and materials for making and using nuclease resistant antisense oligonucleotides to inhibit the expression of TGF-β2 in a cell in vivo to treat hyperproliferative diseases such as cancer in a subject (claim 17, and supporting disclosure). Monia et al. taught the association between TGF-β2 expression and various forms of cancer (paragraph 12), including melanoma, stating the prior art had disclosed that TGF-beta 2 was found to be expressed in all uveal melanomas tested and found to correlate with colon cancer progression (par. 12). It is taught the antisense oligonucleotides disclosed therein may be used in diagnostics, therapeutics, and prophylaxis, and that antisense oligonucleotides in general have been employed as therapeutic moieties in the treatment of disease states in animals and man. Antisense oligonucleotide drugs, including ribozymes, have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established that oligonucleotides can be useful therapeutic modalities that can be configured to

be useful in treatment regimes for treatment of cells, tissues and animals, especially humans (par. 50).

Reed et al. suggested that TGF-beta 2 expression in malignant melanoma may be a critical event in the development of deep invasion and metastases in malignant melanoma.

Accordingly, it would have been prima facie obvious at the time of invention to administer any of the anti-TGF-β oligonucleotides disclosed by Schlingensiepen et al. to a subject having melanoma with the reasonable expectation any of the oligonucleotides could effectively treat a melanoma (i.e., skin carcinogenesis) in which TGF-β was involved, as taught by Schlingensiepen et al. In treating melanoma with any of the Schlingensiepen et al. antisense oligonucleotide compounds the practitioner would necessarily obtain all biological effects inherent to the compound, including those recited by the claims, such as inhibition of metastasis. A compound and its properties are inseparable. As evidenced claims 26, 27, 33, and 41 of the instant application, the antisense oligonucleotide of SEQ ID NO:30, and therefore of SEQ ID NO:72, is an oligonucleotide that inhibits the formation of metastases and production of TGF-beta2. As evidenced by claims 28 and 29, which recite the method of claim 23 for treating esophogeal and neurofibroma cancer, the administration of an oligonucleotide within the scope of claim 23, such as that comprising SEQ ID NO:72 (SEQ ID NO:30), will treat esophageal and neurofibroma cancers and inhibit the formation of metastases in such cancers. As evidenced by page 1, line 13, of the specification, TGF-β is in fact a protein whose synthesis is involved in metastasis.

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Claims 23-33 and 39-44 are rejected under 35 U.S.C. 103(a) as being obvious over Schlingensiepen et al. (US 2007/0196269; 10/581547) and, in the alternative, Schlingensiepen et al. (US 2008/0214483; 11/647586), each independently in view of:

1. Schlingensiepen et al. (US Patent 6,455,689) "Antisense-oligonucleotides for transforming growth factor-β (TGF-β)";
2. Reintgen (U.S. Patent 6,153,388);
3. Mintz (U.S. Patent 5,550,316);
4. Paradise et al. (U.S. Patent 4,999,339);
5. Swift (U.S. Patent 5,843,974);
6. Aylward (U.S. Patent 6,787,161);
7. Brandt et al. (U.S. Patent 5,610,280);
8. McCracken (U.S. Patent 5,369,527);
9. Fakhrai et al. (US Patent 6,120,763)"Compositions and methods for enhanced tumor cell immunity in vivo";
10. Monia et al. (US 2004/0006030) "Antisense modulation of TGF-β2 expression";
11. Reed et al. (1994) "Expression of transforming growth factor-beta 2 in malignant melanoma correlates with the depth of tumor invasion. Implications for tumor progression" *Am J Pathol.* Jul;145(1):97-104;

The applied Schlingensiepen et al. (US 2007/0196269; 10/581547) and, in the alternative, Schlingensiepen et al. (US 2008/0214483; 11/647586) references each have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might

be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Schlingensiepen et al. (US 2007/0196269) and Schlingensiepen et al. (US 2008/0214483) each disclosed antisense oligonucleotides and methods of use thereof within the scope of the instant claims for inhibiting TGF-β2 expression and treating skin carcinogenesis in a subject.

Prior art references 1-11 are relied on for the reasons given above in the rejection of claims 28-33, 39-42, and 44 under 35 USC 103. As a whole the prior art reasonably suggested inhibiting the expression/production of TGF-β2 using antisense oligonucleotides to treat various forms of cancer, including melanoma, as implied by Schlingensiepen et al. in each of the applications above.

Accordingly, the instant methods would have been prima facie obvious at the time.

Response to Arguments

Applicant's arguments traversing the rejections of the claims over the Schlingensiepen et al. references under 35 USC 103 as they may bear on the new rejections above, have been fully considered but are not persuasive.

Applicant appears to argue the patentability of the claims depend on the absence of evidence and knowledge in the prior art that melanoma was a well recognized form of skin

cancer. The Examiner disagrees and provides several references herewith in support of this position.

Applicant argues none of the Schlingensiepen et al. references cited herein disclose an antisense for treatment of formation of metastases. This fact is immaterial to the rejection. The references as a whole suggested a method for treating melanoma that included each and every step and material limitation of the instant claims. As evidenced by the claims themselves, the oligonucleotides of Schlingensiepen et al. have anti-metastatic properties, and the fact that the prior art does not expressly recognize these anti-metastatic properties is irrelevant because it does not distinguish the method claimed from that suggested by the prior art. "The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995).

Furthermore, the inhibitory effect is always present, whether or not the cancer is or has metastasized. Accordingly, the method suggested by the prior art meets all the limitations in the claims, including the functional limitation of inhibiting metastases. Applicant presents no

evidence to show any of the oligonucleotides disclosed by any of the Schlingensiepen et al. references do not inhibit the formation of metastases.

Additionally, claims 39-42 do not require inhibition of metastasis formation or treatment of metastases, but merely treatment of any of the cancers listed.

Applicant's remarks alleging specific deficits in each of Fakhrai, Monia, and Reed have been fully considered but are not persuasive. To be sure, Fakhrai and Monia explicitly and implicity disclosed using antisense oligonucleotides targeted to TGF-β2 for the treatment of melanoma. Taken with Schlingensiepen et al., who disclosed an antisense identical to SEQ ID NO:30 for inhibiting TGF-β and for treating skin carcinogenesis involving TGF-β, the evidence clearly and precisely suggested the instantly claimed methods for treating melanoma.

With regard to Reed et al., the instant claims are not limited to melanomas expressing TGF-β. Accordingly, Applicant argues a limitation not found in the claims. Further, Reed et al. expressly concluded based on their results that TGF-β2 expression in malignant melanoma may be a critical event in the development of deep invasion and metastases in malignant melanoma (abstract). One of skill would therefore reasonably infer the correlation, and in seeking to apply the anti-cancer methods of Schlingensiepen et al. would understand the method is directed to tumors expressing reasonably assay for TGF-β2 expression. One of skill would therefore take reasonable steps to check for TGF-β2 expression in the melanoma to ensure the method was appropriate.

***

Claims 28-32, 39, 40, 42, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (US 2004/0006030) as applied to claims 23-25 and 43 above, and

further in view of Fakhrai et al. (US Patent 6,120,763) "Compositions and methods for enhanced tumor cell immunity in vivo"; and Fakhrai et al. (U.S. Patent 7,101,543).

Monia et al. is relied for the reasons given above in the rejection of claims 23-25 and 43 under 35 USC 102(e).

Monia et al. does not specifically teach treating any of the particular cancers listed in claims 28-30, such as melanoma or lung cancer.

However, it would have been prima facie obvious, and one of skill would reasonably have predicted, that antisense oligonucleotides targeting TGF-β2, such as any of those disclosed by Monia et al., could be used to treat melanoma and inhibit the growth of melanoma cells, given that Fakhrai et al. (US Patent 6,120,763) claimed and enabled a method for prolonging the survival of a subject having melanoma comprising administering genetically modified cells that express an antisense oligonucleotide that targets and inhibits the expression of TGF-β2 (claims 1-10; Example II), and given that Fakhrai et al. (U.S. Patent 7,101,543) claimed and enabled a method for prolonging survival of a subject having a lung cancer comprising the step of administering to said subject a composition comprising a therapeutically effective amount of genetically modified cells containing a genetic construct expressing a TGFβ-2 inhibitor effective to reduce expression of TGFβ-2 (claims 16-30). It is noted that claims 28, 29, and 44 expressly recite lung cancer.

Applicant's remarks filed 3/18/2010 specially addressing Fakhrai et al. are noted. One of skill would immediately have recognized that the antisense oligonucleotide that inhibits TGF-β2 is the active agent responsible for the cancer treatment effect, and that the means by which the antisense is introduced or delivered is simply an expedient and a matter or design choice to

maximize and sustain antisense-mediated inhibition of the target gene. Accordingly, one of skill would reasonably have expected that any effective means known in the art for delivering an antisense oligonucleotide into a subject in an amount effect to reduce TGF-β2 production as required for cancer treatment would produce substantially the same effect as that disclosed by Fakhrai et al., given that Monia et al. disclosed and recommended numerous such routes by which to deliver an oligonucleotide.

All effects inherent to the use of antisense oligonucleotides that inhibit TGF-β2, including those recited in the instant claims, such as inhibition of metastasis formation, would necessarily be obtained by the administration of such oligonucleotides, since a compound and its properties are inseparable, and since, as evidenced by instant claim 25, the inhibition of TGF-β2 inhibits formation of metastases (MPEP 2112).

Response to Applicants' Arguments

Applicants' arguments presented on 3/18/2010 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
July 13, 2010